

**EDITORIAL COMMENT**

# Atrial Functional Mitral Regurgitation

## The Left Atrium Gets its Due Respect\*

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*My psychiatrist told me I was crazy and  
I said I want a second opinion.**He said okay, you're ugly too.*

—Rodney (“no respect”) Dangerfield (1)

Moderate or greater mitral regurgitation (MR) is the most frequent valve disease in the United States, with a prevalence (exceeding 2 million people in 2002) that is anticipated to double by 2030 (2,3). Competence of the mitral valve requires a temporally and spatially coordinated interaction of the mitral leaflets with the annulus, chordae tendinae, and papillary muscles; dysfunction of any of these components will affect the normal systolic coaptation of the anterior and posterior leaflets and cause mitral regurgitation. Mechanistically, MR is classified as either primary (i.e., intrinsic valve disease) or functional, and is further subclassified by the degree of leaflet mobility. Functional MR occurs in patients with a structurally normal valve (generally with restricted leaflet mobility), mitral annular dilation, and left ventricular remodeling (4); whether annular dilation alone (no left ventricular [LV] remodeling, normal leaflet mobility) is sufficient for the development of MR is controversial.

**See page 1474**

The mitral annulus is a thin, discontinuous, fibrofatty ring that geometrically resembles a hyperbolic paraboloid that is bordered by insertions of atrial and ventricular myocardium (5). The nonplanarity and shape of the annulus reduce mechanical stress on the leaflets, and the sphincteric contraction by the associated myocardial fibers reduces annular area ~25% during the cardiac cycle, thereby facilitating normal leaflet coaptation (6). The posterior annulus is in contact with both left atrial myocardium and the base of the

posterior mitral leaflet (5); accordingly, left atrial enlargement may contribute to the development of MR by exerting tension on the posterior leaflet and by altering the planarity of the mitral annulus. Moreover, anterior mitral leaflet musculature of atrial origin may modulate leaflet stiffness and help timely valve closure (7). Interestingly, phenol ablation of the annular and leaflet musculature on the atrial side of the valve in sheep with normal LV geometry results in a reduction in pre-systolic annular area, delayed mitral valve closure, and a change in shape of the anterior mitral leaflet during valve closure, suggesting that atrial myocardium influences the 3-dimensional geometry and function of the annulus and anterior mitral leaflet (8).

Despite these animal data, echocardiographic studies in humans with lone atrial fibrillation (i.e., normal LV size and function) have concluded that isolated annular dilation does not lead to significant MR (9–11). For example, Otsuji et al. (9) found that compared with patients with ischemic cardiomyopathy and significant MR, patients with lone atrial fibrillation (AF) and a similar degree of annular enlargement had only modest MR (regurgitant fraction:  $36 \pm 25\%$  vs.  $-3 \pm 8\%$ ); in a multivariate analysis, posterior mitral leaflet tethering length, but not mitral annular enlargement, was an independent contributor to moderate or greater MR. These data confirm the notion that significant functional MR requires LV remodeling–generated leaflet distortion in addition to annular enlargement. Indeed, progression or recurrence after annuloplasty for functional MR relates modestly to annular dilatation but strongly to mitral leaflet tenting that is a function of ventricular remodeling, papillary muscle displacement, and increased chordal traction (4). Although leaflet tenting (and the resultant incomplete mitral leaflet closure) is most responsible mechanistically, mitral valve prolapse and altered mitral annular dynamics have been implicated in ischemic functional MR (12,13).

In this issue of the *Journal*, Gertz et al. (14) test the hypothesis that significant functional MR in patients with lone AF may be caused solely by left atrial enlargement and annular dilation produced by atrial remodeling. Patients referred for a first AF ablation who had both a baseline echocardiogram and 1-year clinical follow-up, normal LV systolic function, and at least moderate mitral regurgitation (the “MR cohort”) were compared with a control “reference cohort” with mild MR or less, selected from the same group of referents (14). Importantly, the MR cohort was older and more frequently hypertensive. Not surprisingly, these patients more often had persistent than paroxysmal AF, and had a larger left atrium and mitral annulus than controls. Interestingly, in patients with follow-up echocardiograms (32 of 53 patients), maintenance of sinus rhythm resulted in greater reductions in left atrial volume and mitral annular diameter and less MR than those whose arrhythmia recurred. These data support the authors’ hypothesis that AF may be associated with an “atrial functional MR” (as

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opposed to functional MR as a result of ventricular remodeling) of at least moderate severity. Although the authors imply tacitly that atrial functional regurgitation produces significant MR, it is likely that mild functional MR is a common complication of atrial fibrillation. In that regard, a trivial, albeit statistically significant, increase in MR severity was noted in the controls whose arrhythmia recurred.

Although the notion that AF and resultant left atrial and (especially) annular dilation may be the cause of functional MR is not itself novel (15–18), these earlier and smaller studies argue convincingly for an association, not a causal relationship. The study by Gertz et al. (14) is distinctive in that the salutary changes after ablation in the MR cohort (but also in the reference cohort) make a compelling case for causation. Although the improvement in MR severity and left atrial enlargement in the recurrence group is unexplained, 1 hypothesis that warrants testing is that the overall burden of AF was reduced in both groups. The fact that 24% of patients in sinus rhythm still had moderate or severe MR at follow-up suggests that AF, although reduced, was not eliminated. The use of continuous electrocardiographic monitoring would help resolve both of these issues.

These data are provocative and conflict with conventional dogma, and accordingly, need to be interpreted with a clear understanding of the study limitations. The authors recognize the biases inherent in their retrospective study design and the difficulties arising from incomplete data collection; there is also a need to consider the patient's age, the influence of concomitant medications and disease severity, and referral biases. Although the method used to estimate the severity of MR (i.e., color flow jet area) is an acknowledged limitation, the relevance to this investigation is somewhat understated and warrants emphasis. Color flow jet area provides a rapid screening of the presence and direction of the regurgitant jet and a semiquantitative assessment (at best) of its severity. Although a larger area may reflect more significant regurgitation, the sole reliance on a single-frame measurement of jet size (either alone or, as in this case, normalized for left atrial size) can be quite misleading, as anatomic, physiological (especially left atrial size and compliance), and instrument factors, such as pulse repetition frequency, color gain, and transducer frequency, all significantly impact regurgitant jet size (19,20). Color flow area is also influenced by the momentum of flow, which is the product of flow rate and velocity; because of this, a jet may appear larger by increasing the driving pressure (in this instance, systolic systemic blood pressure) across the valve. Thus, hypertensive patients with mild MR may have a large jet area. Thus, a critical point for future studies is that the evaluation of MR severity should be quantitative and integrate multiple parameters, rather than being dependent on a single measurement (19). In this regard, the authors correctly caution that the findings "should be considered hypothesis-generating only" (14).

The precise mechanism(s) of atrial functional mitral regurgitation are not clear. Atrial fibrillation may produce

MR by the effects that fibrillation-induced atrial remodeling has on atrial function and synchrony, and annular size, geometry, and function. Changes in the ratio of leaflet area to annular area, alterations in the normal geometric relations between the leaflets and annulus, and the potential effects of atrial musculature on the shape of the annulus and mechanical forces on the leaflets may all be operative. Moreover, although the atrial remodeling process is essentially equated with mitral annular remodeling, reverse atrial remodeling following successful ablation may have improved atrial asynchrony and increased atrial systolic function as was shown after cardioversion for persistent atrial fibrillation (21).

The prognosis of (ventricular) functional MR is incompletely defined, but is poor even with modest degrees of regurgitation, and surgical outcomes are not optimal (4). An understanding of the natural history of atrial functional MR is inchoate, although the data from Gertz et al. (14) suggest that reducing the burden of atrial fibrillation decreases the severity of regurgitation. The implications of these findings are highly relevant, considering the debate of rate versus rhythm control of AF (22). It is also unknown whether the prognosis is different in patients with AF with than without atrial functional MR; however, there is some suggestion that it is (17).

Finally, the prevalence of atrial functional regurgitation is uncertain. Although infrequently described, given the epidemic increase in the incidence of AF (23), the 6.5% incidence in this select group of patients referred for their first ablation suggests that atrial functional MR is not rare. Clearly, the mechanism of atrial functional MR and its clinical significance must be understood in additional studies using more quantitative methods. Real-time 3-dimensional echo of the annulus and the coaptation line to study geometry and function of the annulus and its relation to the leaflets may be a useful method in this regard (24). Until then, the concept of atrial functional regurgitation provides an intriguing, but untested, rationale for aggressive rhythm control of AF. Nevertheless, the left atrium seems to be getting the respect that it deserves.

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